PRAD-1/Cyclin D1 Gene Overexpression in Chronic Lymphoproliferative Disorders: A Highly Specific Marker of Mantle Cell Lymphoma

By Francesc Bosch, Pedro Jares, Elias Campo, Armando Lopez-Guillermo, Miguel Angel Piris, Neus Villamor, Dolores Tassies, Elaine S. Jaffe, Emilio Montserrat, Ciril Rozman, and Antonio Cardesa

The t(11;14)(q13;q32) translocation and its molecular counterpart bcl-1 rearrangement are frequently associated with mantle cell lymphomas (MCLs) and only occasionally with other variants of B-cell lymphoid malignancies. This translocation seems to activate the expression of PRAD-1/cyclin D1 gene located downstream from the major breakpoint cluster region of this rearrangement. However, the possible overexpression of this gene in other lymphoproliferative disorders independently of bcl-1 rearrangement is unknown. We have examined the overexpression of PRAD-1 gene in a large series of 142 lymphoproliferative disorders including 20 MCLs by Northern blot analysis. Cytogenetic and/or bcl-1 rearrangement analysis with 2 probes (MTC, p94PS) were performed in 28 cases. Strong PRAD-1 overexpression was observed in 19 of the 20 MCLs including 3 gastrointestinal forms and 4 blastic variants. t(11;14) and/or bcl-1 rearrangement was detected in 6 of the 12 MCLs examined. No correlation was found between the different levels of mRNA expression and the pathologic characteristics of the lymphoma. Among chronic lymphoproliferative disorders other than MCL, only 1 atypical chronic lymphocytic leukemia (CLL) with a t(11;14) translocation and bcl-1 rearrangement and the 2 hairy cell leukemias (HCLs) analyzed showed upregulation of PRAD-1 gene. The expression in the 2 HCLs was lower than in MCL, and no bcl-1 rearrangement was observed. These findings indicate that PRAD-1 overexpression is a highly sensitive and specific molecular marker of MCL but it may also be upregulated in some B-CLLs and in HCL.

© 1994 by The American Society of Hematology.

From the Postgraduate School of Hematology “Farreras Valentí” and the Department of Anatomic Pathology, Hospital Clinic, University of Barcelona, Barcelona; the Department of Basic Medical Sciences, University of Lleida, Lleida; the Department of Anatomic Pathology, Hospital “Virgen de la Salud”, Toledo, Spain; and the Hematopathology Section, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD.

Submitted May 17, 1994; accepted June 24, 1994.

Supported by Grant No. SAF 1195/93 from DGICYT, Ministerio de Educación y Ciencia, and Grant No. 93/0303 and 94/1035 from Fondo de Investigaciones Sanitarias de la Seguridad Social, Ministerio de Sanidad y Consumo, Spain. P.J. holds Research Fellowships from the Hospital Clinic of Barcelona, and the Postgraduate School of Hematology Farreras-Valentí and Schering Plough, Spain. P.J. is a fellow supported by the Spanish Ministerio de Educación y Ciencia.

Address reprints to Elias Campo, MD, Department of Anatomic Pathology, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. section 1734 solely to indicate this fact.

© 1994 by The American Society of Hematology.

2726

Blood, Vol 84, No 8 (October 15), 1994: pp 2726-2732

From www.bloodjournal.org by guest on October 23, 2017. For personal use only.
Table 1. Tissue Samples and Results of Northern Blot Analysis

<table>
<thead>
<tr>
<th>Tissue Samples</th>
<th>No. of Cases</th>
<th>PRAD-1/cyclin D1 Overexpression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign lymphadenopathy</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Hodgkin’s disease</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>B-cell lymphoproliferative disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLL</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Typical</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>CLL/PLL</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>HCL</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoplasmacytoid</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>MCL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diffuse</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Blastic variant</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>LCL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Mixed</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>SMZL</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Myeloma</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>T-cell lymphoproliferative disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoblastic lymphoma</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral T-Cell lymphoma</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>142</td>
<td>22</td>
</tr>
</tbody>
</table>

Abbreviation: PL, prolymphocytic leukemia. * One case was a Richter’s syndrome.

MATERIALS AND METHODS

Tissue and cell samples. A total of 146 specimens from 142 patients with different lymphoproliferative disorders was included in the study on the basis of the availability of snap-frozen samples for molecular studies. These cases were obtained from the files of the Departments of Pathology at the Hospital Clinic, University of Barcelona (Barcelona) and Hospital Virgen de la Salud (Toledo, Spain).

The cases included in the study (see Table 1) were 9 benign reactive lymphadenopathies, 5 Hodgkin’s diseases (3 nodular sclerosis and 2 mixed cellularity), 52 B-CLLs, 2 hairy cell leukemias (HCLs), 5 lymphoplasmacytoid lymphomas, 8 follicular lymphomas, 20 MCLs including 3 cases located in gastrointestinal (GI) mucosa (3 nodular, 13 diffuse, and 4 blastic variants), 20 LCLs, 3 immunoblastic lymphomas (one being a Richter’s syndrome), 1 Burkitt’s lymphoma, 3 GI mucosa-associated lymphoid tissue (MALT) lymphomas, 6 splenic marginal zone lymphomas (SMZLs), 3 myelomas, and 5 T-cell lymphomas (1 lymphoblastic, 2 peripheral T-cell, and 2 mycosis fungoides). The tissue sources consisted of 92 lymph nodes, 9 spleens, 6 GI specimens, 1 tonsil, and 38 cell suspensions from peripheral blood (PB). The cases were classified using both the Working Formulation and the Kiel classification. PB smears from the B-CLLs and HCLs were also reviewed. B-CLLs were classified according to the French-American-British (FAB) criteria, being considered as typical (29 cases) when they have more than 90% of small mature lymphocytes. Atypical cases included the FAB categories of B-CLL/PLL (3 cases) and B-CLL/mixed (20 cases).

MCLs were classified as nodular or diffuse and typical or blastic variants according to histologic criteria previously described.31,33 Four cases that were initially diagnosed as lymphocytic lymphoma of intermediate differentiation (IDL) but that showed pseudofollicular growth centers with plasmacytoid and paraimmunoblasts were reclassified as atypical B-CLLs with cleaved cells (atypical mixed).31

All the cases were immunophenotyped using immunochemistry on frozen or fixed-paraffin embedded tissue sections and/or cell suspensions by flow cytometry. Although the number of antibodies used varied from case to case, in all the tumors the immunophenotyping included Ig light and heavy chains, and several of the B-cell (CD19, CD20, CD22, CD45RA, CD10, FMCL) and T-cell markers (CD2, CD3, CD5, CD7, CD43, CD45RO) and T-cell markers. In MCLs, CD5, CD10, CD23, CD35, and/or J42/43 for follicular dendritic cells were examined. Cytogenetic analysis was available in 8 cases, including 7 B-CLLs and a blastic variant of MCL.

RNA extraction and Northern blotting analysis. Total cellular RNA was isolated from frozen tissues and cell suspensions by guanidine isothiocyanate extraction and cesium chloride gradient centrifugation.32,33 Eight micrograms of total RNA from each sample was electrophoresed on a denaturing 1.2% agarose gel and transferred to Hybond-N membranes (Amersham, Buckinghamshire, UK). As a positive control, 5 μg of total RNA from a squamous cell carcinoma of the larynx previously known to have PRAD-1 gene amplification and mRNA overexpression was included in all the gels. The membranes were prehybridized in 50% formamide, 5X SSC; 1X SSC is 0.15 mol/L NaCl and 0.015 mol/L Na citrate, pH 7.2, 1X Denhardt’s, 100 μg/mL denatured salmon sperm DNA, and 1% sodium dodecyl sulfate (SDS) at 42°C for 6 hours and hybridized overnight with the [α-32P]dCTP-labeled PRAD-1 cDNA probe. Washes after hybridization included a final step under stringent conditions in 0.1X SSC and 0.1% SDS at 65°C for 30 minutes. The filters were then autoradiographed using intensifying screens at −70°C for 48 to 72 hours. Longer exposures (2 to 3 weeks) were also taken to observe possible baseline signals.

Hybridization signals of different radiolabeled exposures within the linear response range were quantified using a UVP-GDS5000 video densitometer (UVP, Inc, San Gabriel, CA). The hybridization signals of each case were normalized to the respective 28S RNA band for loading differences and to the signal of the same control case present in all the blots to standardize expression levels. Expression is presented as arbitrary units related to the expression of the control case.

DNA extraction and Southern blotting analysis. DNA extraction could be performed from additional frozen material available in 21 cases (11 MCLs, 2 HCLs, 6 B-CLLs, 1 LCL, and 1 SMZL). High molecular weight DNA was obtained by the standard proteinase K/RNase treatment and phenol-chloroform extraction as described previously.35 DNA from each case (10 μg) was digested with EcoRI, HindIII, and BamHI restriction enzymes (BRL, Gaithersburg, MD). The digested DNA was separated on 0.8% agarose gels and transferred to nylon membranes (Hybond-N; Amersham) according to the method of Southern.36 The membranes were prehybridized with 50% formamide, 5X SSC, 1X Denhardt’s, 100 μg/mL denatured salmon sperm DNA, and 1% SDS at 42°C for 6 hours and hybridized with 50% formamide, 5X SSC, 1X Denhardt’s, 100 μg/mL salmon sperm DNA, 10% dextran sulfate, 1% SDS, and 10% ppm/mL of [α-32P]dCTP-labeled probe for 24 hours. After hybridization, membranes were washed with 2X SSC and 0.1% SDS at room temperature for 30 minutes followed by 2X SSC and 0.1% SDS at 60°C for 1 hour and 0.1X SSC and 0.1% SDS at 60°C for 1 hour. The filters were then autoradiographed using intensifying screens at −70°C.

Probes. Probes were radiolabeled using a random primer DNA labeling kit (Promega Corp, Madison, WI) with [α-32P]dCTP. The PRAD-1/cyclin D1 probe used was 1.4-kb EcoRI fragment (XM-14)
of the pPL-8 partial cDNA clone of PRAD-1 gene (kindly provided by Dr A. Arnold, Massachusetts General Hospital, Boston, MA). Southern blots were hybridized with two bcl-1 translocation breakpoint probes including a 2.3-kb Sac I fragment for the MTC (kindly provided by Dr Y. Tsujimoto, Wistar Institute, Philadelphia, PA) and a 460-bp Sma I-BamHI DNA fragment from p94PS (kindly provided by Dr T. C. Meeker, University of California, San Francisco, CA).

RESULTS

The results of Northern blot analysis performed in the 142 cases studied are summarized in Table 1. PRAD-1/cyclin D1 overexpression was observed in 19 of the 20 (95%) MCLs examined. These cases included 12 diffuse MCLs, 3 GI MCLs, and the 4 blastic variants of MCL (Table 2, Fig 1). In 2 cases (nos. 2 and 16; see Table 2), different tissue samples were analyzed (lymph nodes, spleen, and tonsil), and overexpression was detected with similar levels in all of them. The only negative MCL had a typical diffuse morphology and immunophenotype with expression of B-cell markers, CD5 antigen, and presence of a prominent meshwork of follicular dendritic cells.

Only 3 non-MCLs showed PRAD-1 overexpression (see Table 2 and Fig 1). These cases included 1 of the 52 B-CLLS examined (case no. 20) and the 2 HCLs. Interestingly, none of the 4 cases of atypical B-CLL previously diagnosed as IDL showed overexpression of this gene. The overexpressed B-CLL case was an atypical B-CLL with a t(11;14)(q13;q32) and bcl-1 rearrangement with the p94PS probe. PB showed a high white blood cell (WBC) count (450 to 1,000 \( \times 10^9 \) cells/L) with less than 80% to 90% small lymphocytes and 10% to 20% of prolymphocytes and small cleaved cells. A lymph node biopsy specimen showed involvement consistent with the diagnosis of B-CLL. Immunophenotype study was positive for CD19, CD5, CD22, CD25, FMC7, \( \lambda \) chain, IgD, and IgG antigens and was negative for CD10, CD23, and \( \kappa \) chain markers. PRAD-1/cyclin D1 overexpression was shown in the PB sample and in the spleen and lymph node biopsy specimens. The patient died with a transformation of his disease to a high grade malignant lymphoma (Richter's syndrome). On the other hand, the clinical and pathologic manifestations, immunophenotype, and evolution of the 2 overexpressed HCLs were characteristics of this disorder.

No overexpression was observed in any of the benign lymphadenopathies (9 cases), the Hodgkin's diseases (5 cases), or the other 105 NHLs analyzed (Table 1). Thus, PRAD-1/cyclin D1 overexpression was shown in 19 of 20 (95%) MCLs and in only 3 of 113 (2.7%) non-MCLs.

The PRAD-1 signal in most of the overexpressed cases showed two transcripts of 4.5 and 1.5 kb, as previously described. However, the intensity of the smaller transcript was frequently higher than the 4.5-kb message (see Fig 1 and Table 2; mean 1.5 kb/4.5 kb = 2.1). Three overexpressed cases, 2 MCLs and the atypical B-CLL, showed insignificant
levels of the 4.5-kb message and anomalous transcripts of 2.5-kb and 3.2-kb in addition to the normal 1.5-kb message (Fig 1).

The levels of PRAD-1/cyclin D1 expression assessed by densitometric analysis were heterogeneous (Table 2). In MCLs, the expression varied from 0.3 to 6.6 arbitrary units (mean, 1.64). No correlation was found between the mRNA levels and the pathologic characteristics of the MCLs. Blastic variants of MCL had a higher mitotic index (median, 6.8; range, 3.2 to 9.4 mitosis per high power field [HPF]) than the typical MCL (median, 0.5; range, 0.1 to 1.6 mitosis per HPF). In addition, patients with blastic variant of MCL showed a shortened survival than that of the patients with typical MCL (median survival, 14 v 52 months; P = 0.015). However, the PRAD-1/cyclin D1 mRNA levels in both groups of patients were similar (mean, 1.7 v 1.6 arbitrary units, respectively). No significant differences in survival were observed in the series according to the PRAD-1/cyclin D1 mRNA levels.

The only positive B-CLL had an anomalous transcript of 2.5 kb and, similar to the other 2 MCLs (cases no. 14 and 16) with anomalous transcripts, showed the highest levels of PRAD-1 message among all the cases of this study (2.8, 6.6, and 2.4 arbitrary units, respectively; see Table 2). The 2 HCLs examined disclosed significantly lower levels of expression than the MCL (Table 2).

Negligible baseline expression of PRAD-1 was observed in almost all the cases studied, including reactive lymphadenopathies, when blots were overexposed for long periods of time (2 to 3 weeks). To determine whether this very low signal is due to expression in lymphoid or stromal cells would require in situ hybridization or immunohistochemical studies.

Cytogenetic analysis was performed in 8 cases. Two cases showed the t(11;14)(q13,q32), 1 atypical B-CLL (case no. 20) and 1 blastic MCL (case no. 15). PRAD-1 was overexpressed in both cases. DNA was available for Southern blot analysis in 11 cases of MCL, 6 B-CLLs, 1 LCL, 1 SMZL, and 2 HCLs. bcl-1 rearrangement was detected in 5 MCLs with MTC probe and in the atypical B-CLL (case no. 20) with the p94PS probe. No rearrangement was observed in any of the other cases. All the rearranged cases showed PRAD-1 upregulation (Table 2).

DISCUSSION

The findings of the present study confirm the constant overexpression of the PRAD-1/cyclin D1 gene in MCLs (19 of 20 cases) and indicate that upregulation of this gene in lymphoproliferative disorders is a highly specific molecular marker of this lymphoma. These results are consistent with those previously reported by Rosenberg et al21 and Rimokh et al,29 who overall found PRAD-1/cyclin D1 gene overex-
expression in 22 of the 23 MCLs analyzed. However, the number of chronic lymphoid malignancies other than MCL included in these previous reports was limited. In our study, we examined 113 non-MCLs and 9 reactive lymphadenopathies, and PRAD-1/cyclin D1 upregulation was found in 3 chronic lymphoid malignancies (2.7%) and in none of the reactive lymphadenopathies. This high prevalence and specificity of PRAD-1 overexpression in MCL strongly suggest that deregulation of this gene plays an important role in the pathogenesis of this lymphoma.

Previous studies have shown a strong association between bcl-1 rearrangements and MCL. This rearrangement has been detected in up to 73% of cases studied using several probes spanning the 110-kb distance between the bcl-1 major breakpoint region and the PRAD-1 gene. In our series, 58% of the MCLs examined showed a t(11;14) translocation or bcl-1 rearrangement. The fact that overexpression was found more frequently than bcl-1 rearrangement is most likely because of the existence of additional breakpoints outside the sites detected with the available probes. Alternatively, the existence of mutations in regulatory elements of PRAD-1 gene has also been suggested. The importance of rearrangements in deregulating PRAD-1 in lymphoproliferative disorders is further supported by the fact that the only B-CLL overexpressing the PRAD-1 gene in our series also had a t(11;14) translocation and bcl-1 rearrangement. The low frequency of PRAD-1/cyclin D1 overexpression in non-MCLs detected in this study is consistent with previous observations of bcl-1 rearrangements in less than 5% of these cases.

The levels of PRAD-1/cyclin D1 expression varied from case to case. However, the differences in expression did not correlate with the pathologic characteristics of the MCLs. Particularly, blastic variants which have higher proliferative activity and significant shortened survival did not show higher levels of expression. This finding suggests that other mechanisms may cooperate with overexpressed cyclin D1 in the control of cell proliferation and tumor progression in these neoplasms.

The possible significance of the different ratios of expression between the 4.5 and 1.5 kb messages observed in our study is not known. Both mRNAs contain the whole coding region of the gene and differ in the length of the 3' untranslated region. It has been postulated that different translactions might influence the ratio of these transcripts. The predominance of the 1.5-kb message and the presence of aberrant transcripts seems to be a characteristic of lymphoid neoplasms, because they have not been described in breast or squamous cell carcinomas. In our experience, we have not observed anomalous transcripts in a large series of 96 breast and squamous cell carcinoma of the larynx examined for PRAD-1 overexpression (Jares et al. and P. Jares, unpublished observations). Interestingly, the highest levels of expression in the present study were found in the 3 cases with transcripts of anomalous sizes. High expression of anomalous mRNAs have been also described in some lymphoid cell lines and in occasional MCLs. Molecular analysis of one of these anomalous transcripts showed the loss of AUUUA destabilizing signals at the 3' region that could lead to a longer half-life of the message.

The high specificity and sensitivity of PRAD-1/cyclin D1 expression in MCL may aid in the differential diagnosis of this entity from other low grade NHLs with similar morphology, such as B-CLL with cleaved cells, MALT lymphomas with predominance of centrocyte-like cells, and SMZL. In our study, the 3 MALT lymphomas were negative, whereas the 2 GI MCLs showed high levels of expression. Similarly, the 4 cases initially diagnosed as CD23-negative because of the high number of small cleaved cells, but reclassified as atypical B-CLL because of pseudofollicular growth centers, were also negative. PRAD-1/cyclin D1 expression may also be of value in the separation of the blastic variant of MCL from other large cell and blastic proliferations. This variant was initially recognized to be part of the MCL category based on its morphologic characteristics. These cases have larger cells, higher mitotic index, and shortened survival. In our study, 1 blastic variant (case no.15) carried the t(11;14) translocation, 2 had a bcl-1 rearrangement (cases no. 1 and 16), and all 4 cases overexpressed PRAD-1/cyclin D1. These findings show for the first time that blastic variants have the same cytogenetic and molecular characteristics as typical MCL.

Initial studies identified t(11;14) translocation and/or bcl-1 rearrangement in 0 to 6% of B-CLLs and in 18% of PLLs. A critical review of these cases has led to a reclassification of some of such cases as MCLs, suggesting that, probably, many of the B-CLL cases previously described in association with bcl-1 rearrangement may in fact be MCLs. Although the t(11;14) translocation and bcl-1 rearrangement may be present in some true B-CLLs, such as the case reported in our study, this possibility is extremely rare. The biologic relationship between lymphoproliferative disorders sharing molecular abnormalities similar to those found in MCLs is intriguing. Interestingly, however, our positive case was an unusual B-CLL with a high WBC count and a relatively high mitotic index; this case was also CD23-negative and eventually progressed to a high grade lymphoproliferative disorder. Whether bcl-1 rearrangements with PRAD-1/cyclin D1 overexpression may identify a subset of unusual B-CLLs with a more aggressive biologic evolution should be further investigated.

The finding of PRAD-1/cyclin D1 overexpression in the 2 HCLs analyzed in our study was unexpected. The clinical manifestations of the 2 patients and the morphology and phenotype of the cells were completely typical of this disorder. The levels of expression in both cases were significantly lower than in most of the MCLs but were definitively higher than in all the other lymphomas examined. In both cases, no bcl-1 rearrangement was detected with any of the two probes. To our knowledge, there are no previous reports of t(11;14) translocation or bcl-1 rearrangement in HCLs. It would be important to know if overexpression of PRAD-1/cyclin D1 is a frequent phenomenon in HCL and if bcl-1 rearrangement is the genetic mechanism implicated in the deregulation of the gene. Further studies may elucidate how the overexpression of a cyclin gene involved in the control of the cell cycle may contribute to the pathogenesis of HCL, a disorder with low proliferative activity.

In conclusion, PRAD-1/cyclin D1 overexpression is a highly specific and sensitive molecular marker of MCLs,
although it may be also disregulated in a minor subset of B-CLLS and in HCL. Further studies are needed to better understand the biologic significance of PRAD-1/cyclin D1 expression in these disorders.

ACKNOWLEDGMENT

The authors thank Gemma Aiza and Izrakia Nayach for their excellent technical assistance; Dr F. Aiter and Dr S. Woessner (Hospital Central de l’Alliança, Barcelona, Spain) for cytogenetic analysis; and Dr A. Arnold (Massachusetts General Hospital, Boston, MA), Y. Tsujimoto (Wininst Institute, Philadelphia, PA), and T. C. Meeker (University of California, San Francisco, CA) for the gift of the probes.

NOTE ADDED IN PROOF

Recently, Oka et al.41 have reported similar findings in 58 patients with B-cell lymphoma. PRAD-1/cyclin D1 overexpression was detected in 6 of 8 MCL and in only 1 of 50 other lymphomas.

REFERENCES

17. Bennet JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, Sultan C: Proposals for the classification of chronic


41. Raffeld M, Jaffe ES: bcl-1, t(11, 14), and mantle cell-derived lymphomas. Blood 78:259, 1991 (editorial)


PRAD-1/cyclin D1 gene overexpression in chronic lymphoproliferative disorders: a highly specific marker of mantle cell lymphoma

F Bosch, P Jares, E Campo, A Lopez-Guillermo, MA Piris, N Villamor, D Tassies, ES Jaffe, E Montserrat and C Rozman